Kidney International, Vol. 55 (1999), pp. 299–307

RenaGel®, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone

Eduardo A. Slatopolsky, Steven K. Burke, Maureen A. Dillon, and The RenaGel® Study Group[1]

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, and GelTex Pharmaceuticals, Inc., Waltham, Massachusetts, USA

RenaGel®, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone.

Background. This multicenter, open-label, dose-titration study assessed the safety and efficacy of RenaGel®, a nonabsorbed calcium- and aluminum-free phosphate binder, in lowering serum phosphorus. Secondary outcomes were its effects on serum intact parathyroid hormone (iPTH) and serum lipids.

Methods. Phosphate binders were discontinued during a two-week washout period. Patients whose serum phosphorus was more than 6.0 mg/dl during washout were eligible for treatment. RenaGel®, at starting doses of two, three, or four 440 mg capsules three times per day with meals, was administered to 172 hemodialysis patients for eight weeks. RenaGel® could be increased by one capsule per meal every two weeks as necessary to achieve serum phosphorus control. A second two-week washout period followed.

Results. Mean serum phosphorus rose from 6.8 ± 2.0 mg/dl at prewashout to 9.1 ± 2.4 mg/dl at the end of the washout period. It then declined to 6.6 ± 1.9 mg/dl by the end of the eight-week RenaGel® treatment period ($P < 0.0001$). Serum phosphorus increased to 8.0 ± 2.2 mg/dl at the end of the second washout period. The mean dose at the end of RenaGel® treatment was 5.4 g per day. Eighty-four percent of the patients previously used calcium-based phosphate binders. As expected, calcium declined during the initial washout period when calcium-based phosphate binders were discontinued. Mean serum calcium declined from 9.6 ± 1.0 mg/dl at prewashout to 9.1 ± 0.8 mg/dl after washout. It then increased to 9.4 ± 0.9 mg/dl by the end of RenaGel® treatment. Median serum iPTH increased during the two-week washout from 208 pg/ml to 316 pg/ml and then declined to 224 pg/ml at the end of the eight-week treatment period ($P < 0.0001$ vs. end of initial washout). After eight weeks of treatment, RenaGel® reduced mean serum total cholesterol from 171.0 ± 43.1 mg/dl to 145.0 ± 38.7 mg/dl ($P < 0.0001$) and mean serum low-density lipoprotein cholesterol from 102.0 ± 34.9 mg/dl to 75.6 ± 29.4 mg/dl ($P < 0.0001$). High-density lipoprotein cholesterol, triglycerides, and serum albumin did not change.

Conclusions. RenaGel®, a novel and calcium- plus aluminum-free effective phosphate binder, can control serum phosphorus and reduce the levels of PTH and cholesterol without inducing hypercalcemia or other side effects. Thus, this new phosphate binder may be effective in the treatment of renal osteodystrophy in uremic patients.

In patients with advanced renal failure, the hyperphosphatemia that develops is associated with severe complications, including metastatic calcification, secondary hyperparathyroidism, and osteitis fibrosa cystica, a bone disease responsible for significant morbidity [1, 2]. Control of dietary phosphate absorption in this population is essential for the prevention of these deleterious sequela. Usually, patients with end-stage renal disease (ESRD) are fed a minimum of 1.0 g of protein per kg of body weight. Thus, it is difficult to restrict the amount of phosphorus in the diet to less than 1,000 mg per day. Because approximately 60% to 70% is absorbed, around 4,000 to 5,000 mg of phosphorus per week enters the extracellular fluid. Most hemodialysis patients are dialyzed three times per week, and roughly 800 mg of phosphorus is removed per treatment [3]. Thus, most well-nourished patients are in positive phosphorus balance. Consequently, approximately 95% of dialysis patients use phosphate binders to reduce dietary phosphorus absorption and achieve serum phosphorus control. The most commonly used phosphate binders contain aluminum or calcium. Aluminum causes neurological, skeletal, and hematologic toxicities in ESRD patients [4–13], whereas calcium can lead to hypercalcemia in some patients as well as soft tissue calcification [14–18]. Because these toxicities limit

[1] Members of the RenaGel® Study Group include the following: Paul Bolin (*Greenville, NC*); Kenneth Boren (*Mesa, AZ*); K. Burke and Maureen Al Dillon (*GelTex Pharmaceuticals, Inc., Waltham, MA*); Douglass T. Domoto (*St. Louis, MO*); Thomas A. Golper (*Little Rock, AR*); Fred Jones (*Raleigh, NC*); C.J. Kaupke (*Orange, CA*); Robert Levinson (*Hollywood, FL*); Michael A. Marx (*Little Rock, AR*); William Mattern (*Chapel Hill, NC*); Mark S. Paller (*Minneapolis, MN*); Maryella D. Sirmon (*Mobile, AL*); Eduardo Slatopolsky (*St. Louis, MO*); Randall Stoltz, (*Evansville, IN*); John Wagner (*New Hyde Park, NY*); Marc Weinberg (*Providence, RI*); Barry Wilkes (*Manhasset, NY*); Duane Wombolt (*Norfolk, VA*); and James van Gelder (*Hollywood, FL, USA*).

Key words: dialysate, renal failure, osteodystrophy, uremia, hyperphosphatemia, bone disease.

Received for publication April 1, 1998
and in revised form July 30, 1998
Accepted for publication August 5, 1998

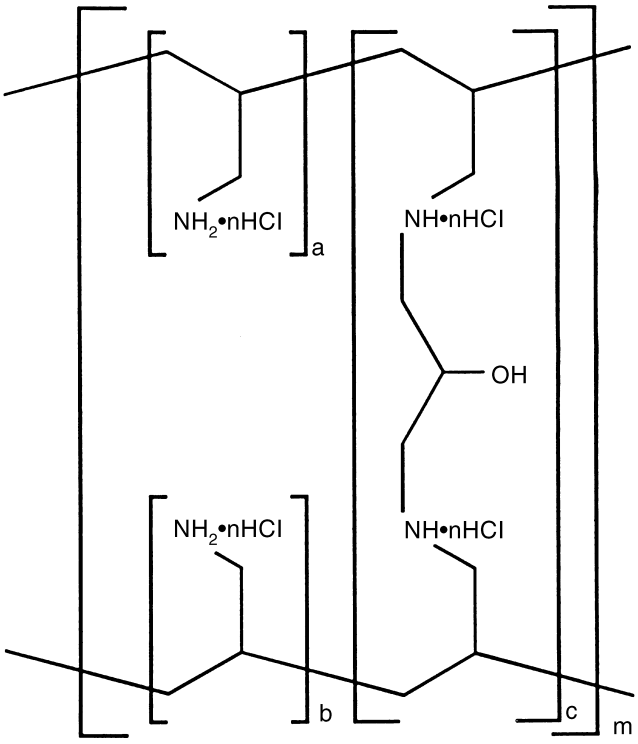

Fig. 1. Structure of RenaGel®, cross-linked poly(allylamine hydrochloride).

utilization of phosphate binders, control of serum phosphorus in many patients is less than optimal. As a result, there is a need for a well-tolerated aluminum- and calcium-free phosphate binder.

This multicenter, open-label, dose-titration study examined the efficacy of RenaGel®, a nonabsorbed calcium- and aluminum-free phosphate binder, in lowering serum phosphorus in hemodialysis patients. RenaGel® is a hydrogel of cross-linked poly (allylamine hydrochloride), which is completely resistant to digestive degradation and is not absorbed from the gastrointestinal tract (Fig. 1). Partially protonated amines spaced one carbon from the polymer backbone interact with phosphate anions by ionic and hydrogen bonds. Preclinical and clinical studies have established the phosphate-binding capacity of RenaGel® and its safety and efficacy in patients with ESRD [19–21].

Objective

The primary objectives of this study were to determine the efficacy of RenaGel® treatment in lowering serum phosphorus and the safety of RenaGel® in hemodialysis patients. The secondary objectives were to assess the effect of RenaGel® treatment on serum intact parathyroid hormone (PTH) and serum lipid profiles in hemodialysis patients.

Table 1. Dietary intake

Dietary intake parameter	Mean	SD
Phosphorus *mg/day*	774.6	291.5
Calcium *mg/day*	414.3	188.7
Vitamin D *μg/day*	5.9	3.9
Total energy *kcal/day*	1358.3	525.9
Total protein *g/day*	57.8	19.7
% Calories from protein	17.7	3.9
Total fat *g/day*	53.4	24.4
% Calories from fat	34.8	6.7
% Calories from carbohydrates	47.5	7.8
Iron *mg/day*	45.3	102.9
Sodium *mg/day*	2094.9	943.3
Potassium *mg/day*	1468.5	686.9
Total vitamin A *μg/day*	953.0	665.6
Total alpha-tocopherol equivalence *mg/day*	13.0	18.2

METHODS

Patients

The study included male and female hemodialysis patients 18 years of age or older treated a minimum of three months with three times per week hemodialysis. Inclusion criteria required stable dosage of an aluminum- or calcium-based phosphate binder for at least one month and, if the patient was on vitamin D replacement therapy, a stable dosage of vitamin D supplementation for at least one month. Over the course of the study, patients were prohibited from consuming antacids containing aluminum or magnesium and were asked to avoid intentional changes in diet. The vitamin D supplementation dose and regimen were maintained unless they needed to be adjusted for safety reasons. Table 1 depicts dietary intake parameters.

Study design

Patients were screened, and administration of calcium- or aluminum-containing phosphate binders discontinued during a two-week washout period (week 1 to 2). Patients who developed hyperphosphatemia (serum phosphorus levels of more than 6.0 mg/dl) during this washout were eligible to receive RenaGel® for eight weeks (weeks 3 to 10). A second two-week washout period followed the end of RenaGel® treatment to establish that serum phosphorus control was due to RenaGel® treatment (weeks 11 to 12).

RenaGel® was supplied as odorless, tasteless, hard gelatin capsules containing 440 mg RenaGel®. The starting dose was two, three, or four capsules three times per day with meals based on washout serum phosphorus levels (Table 2). The RenaGel® dose could be increased one capsule per meal (three capsules per day) every two weeks as necessary to achieve serum phosphorus control.

Collection of blood samples and dietary intake

Blood samples were collected each week just prior to dialysis after the longest interdialytic interval. All blood

Table 2. Washout serum phosphorus ranges, the corresponding RenaGel starting dose, and the number of patients starting at each dose level

Washout serum phosphorus *mg/dl*	Capsules t.i.d.	Patients	
		N	%
≥6.0 to <7.5	2	43	25
≥7.5 to <9.0	3	38	23
≥9.0	4	87	52

samples were analyzed at SmithKline Beecham Clinical Laboratories (Van Nuys, CA, USA) using standard clinical laboratory methods. iPTH was measured by an immunochemilumetric assay (ICMA assay) (upper limit of normal is 59 pg/ml). Dietary intake was assessed at the University of Massachusetts Medical Center (Worcester, MA, USA) using the 24-hour recall method [22]. The subjects were called at three random times during each of the baseline, washout, and treatment phases. Thus, each subject was interviewed nine times during the 12 weeks of the study. The calls were scheduled to include one dialysis day, one nondialysis day, and a weekend day for each of the study periods.

The protocol was approved by the Human Research Committee at each institution, and informed consent was obtained from each patient.

Statistical methods

Wilcoxon signed rank tests were used to assess changes in dietary intake levels and serum concentrations. A linear regression model was used to identify factors associated with changes in serum phosphorus. Spearman rank correlation was used to examine the relationship between the change in serum phosphorus, calcium, and iPTH. Chi-squared tests were used to test RenaGel® dose level group differences for adverse effects, and Kruskal–Wallis tests were used to test RenaGel® dose level group differences for laboratory data. All statistical analyses were based on two-tailed hypothesis tests, with a significance level of $P > 0.05$. A last-observation carry-forward approach was used to complete missing data.

RESULTS

Patients

A total of 172 patients qualified for RenaGel® treatment. Post-baseline serum phosphorus data were not available for four patients, and consequently efficacy analyses were conducted on 168 patients. In total, 144 patients completed the eight-week treatment period. Twenty-four patients did not complete the eight-week treatment period: 15 patients were discontinued due to an adverse event (Table 3); one patient died of a cardiac arrest; one patient discontinued due to noncompliance; three patients withdrew consent; one patient was lost to follow-up; and three patients discontinued for "other

Table 3. Common adverse events

Adverse event	%
Pain	14.5
Diarrhea	12.8
Nausea	11.6
Dyspepsia	9.3
Chest pain	7.6
Headache	7.6
Infection	7.0
Constipation	7.0
Vomiting	7.0
Dyspnea	7.0
Thrombosis	5.8
Hypotension	4.7
Abdominal pain	4.1
Puritus	4.1
Sepsis	3.5
Flatulence	3.5
Gastrointestinal disorder	3.5
Hypocalcemia	3.5
Asthenia	2.9
Hypertension	2.9
Anorexia	2.9
Hypervolemia	2.9
Peripheral edema	2.9
Dizziness	2.9
Insomnia	2.9
Pneumonia	2.9
Fever	2.3
Arterial anomaly	2.3
Eructation	2.3
Myalgia	2.3
Cough increased	2.3

Table 4. Patient characteristics

Characteristic	
Gender	
Male	64%
Female	36%
Race	
African American	52%
Caucasian	34%
Hispanic	13%
Other	2%
Age *years*	
Mean (range)	53 (18 to 86)
Weight *g*	
Mean (range)	79.8 (25 to 175)
Prior phosphate binder	
Calcium acetate	48%
Calcium carbonate	36%
Aluminum	9%
Aluminum-calcium combination	7%
Etiology of ESRD	
Hypertension	30%
Diabetes mellitus	23%
Nephritis	13%
Polycystic kidney disease	5%
Other	28%

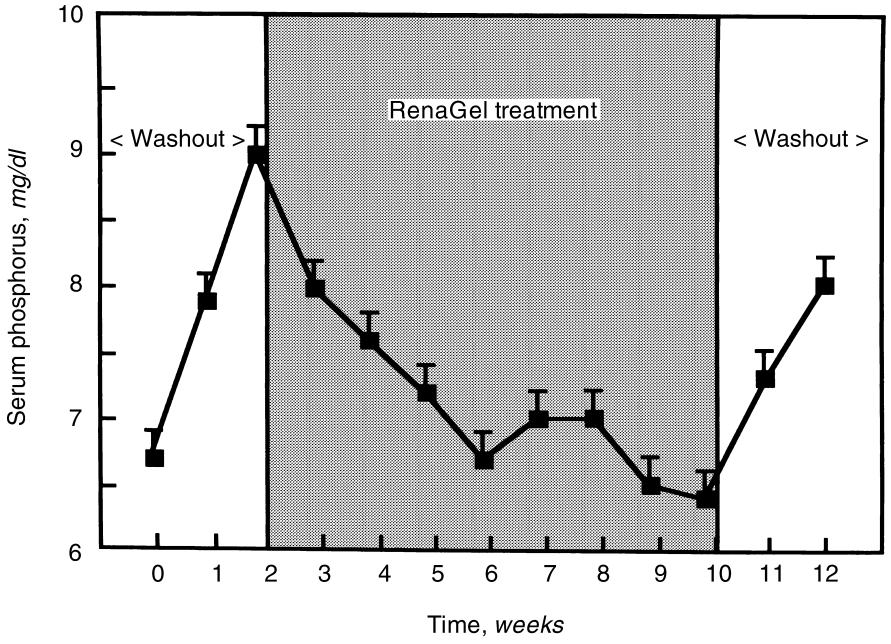

Fig. 2. Effect of RenaGel® on serum phosphorus. During the treatment period with RenaGel the decrease in serum phosphorus 9.1 ± 2.4 to 6.6 ± 1.9 mg/dl was statistically significant ($P > 0.0001$).

reasons." Table 4 summarizes the demographic characteristics of the patient population.

Dosage, compliance, and dietary intake

The mean starting daily dose of RenaGel® was 4.0 g per day, whereas the mean daily dose at the end of the eight-week treatment period was 5.4 g per day. The mean percentage compliance with RenaGel® was 85.1% by pill count. No significant changes in dietary phosphorus and calcium intake occurred during the study.

Serum phosphorus, calcium, and intact parathyroid hormone

Serum phosphorus, calcium, and intact parathyroid hormone (iPTH) levels significantly changed during RenaGel treatment. Figure 2 displays mean serum phosphorus levels throughout the study. Mean serum phosphorus levels increased from 6.8 ± 2.0 mg/dl at prewashout to 9.1 ± 2.4 mg/dl after washout. Upon initiation of RenaGel® treatment, serum phosphorus levels declined immediately and continued declining until the cessation of treatment. Mean serum phosphorus decreased from 9.1 ± 2.4 mg/dl to 6.6 ± 1.9 mg/dl during eight weeks of treatment ($P < 0.0001$). After the post-treatment washout, mean serum phosphorus significantly increased to 8.0 ± 2.2 mg/dl ($P < 0.0001$), establishing that serum phosphorus control was due to RenaGel® treatment. RenaGel® dose was a significant predictor of the decrease in serum phosphorus levels. RenaGel® treatment provided comparable reductions in serum phosphorus for both vitamin D users (2.6 ± 2.5 mg/dl) and nonusers (2.4 ± 2.0 mg/dl).

Figure 3 displays mean serum calcium levels during the study. Mean serum calcium levels decreased from 9.6 ± 1.0 mg/dl at prewashout to 9.1 ± 0.8 mg/dl after washout. Mean serum calcium levels increased to 9.4 ± 0.9 mg/dl following eight weeks of RenaGel® treatment ($P < 0.0001$). After a second two-week washout, mean serum calcium significantly decreased to 9.2 ± 0.9 mg/dl ($P = 0.0132$). Changes in serum calcium were similar between vitamin D users and nonusers.

The mean calcium–phosphate product (Fig. 4) increased from 64.7 to 82.1 mg^2/dl^2 at the end of the washout period. Mean calcium–phosphorus product decreased to 59.8 mg^2/dl^2 after eight weeks of RenaGel® treatment. Subsequently, after discontinuing RenaGel®, mean serum calcium–phosphate product increased to 74 mg/dl.

Median serum iPTH levels over the course of the study are displayed in Figure 5. The median values were chosen for display because the distribution of iPTH data was skewed by a subset of patients with extreme elevations in iPTH. Median serum iPTH levels increased during the washout period from 208 pg/ml to 316 pg/ml. Upon initiation of RenaGel® treatment, median serum iPTH levels declined immediately, reaching 224 pg/ml by the end of the eight-week treatment period ($P < 0.0001$). After two weeks of a second washout, median serum iPTH increased to 307 pg/ml ($P < 0.0001$). RenaGel® treatment lowered median iPTH levels in both vitamin D users and nonusers. There was no significant difference in PTH levels between the prewashout measurement and the end of the treatment measurement ($P = 0.1567$).

Serum lipids

RenaGel® treatment significantly reduced mean serum total cholesterol (Fig. 6) from 171.0 ± 43.1 to 145.0

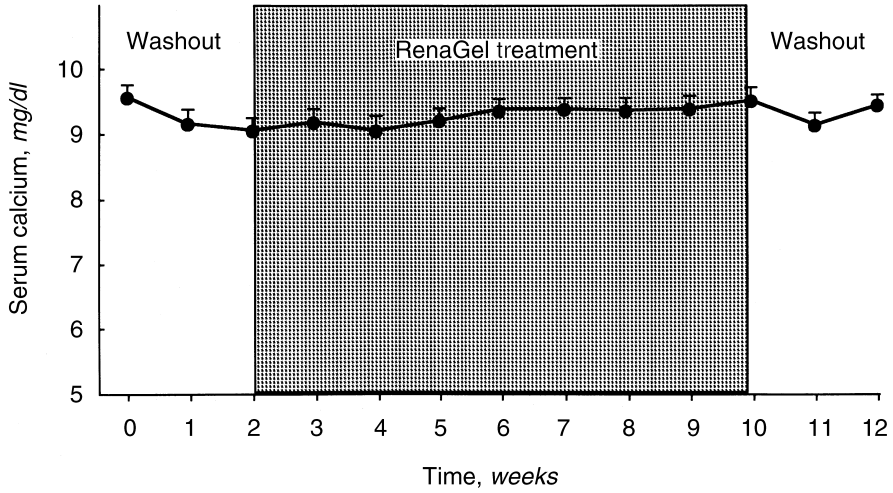

Fig. 3. Effect of RenaGel® on serum calcium.

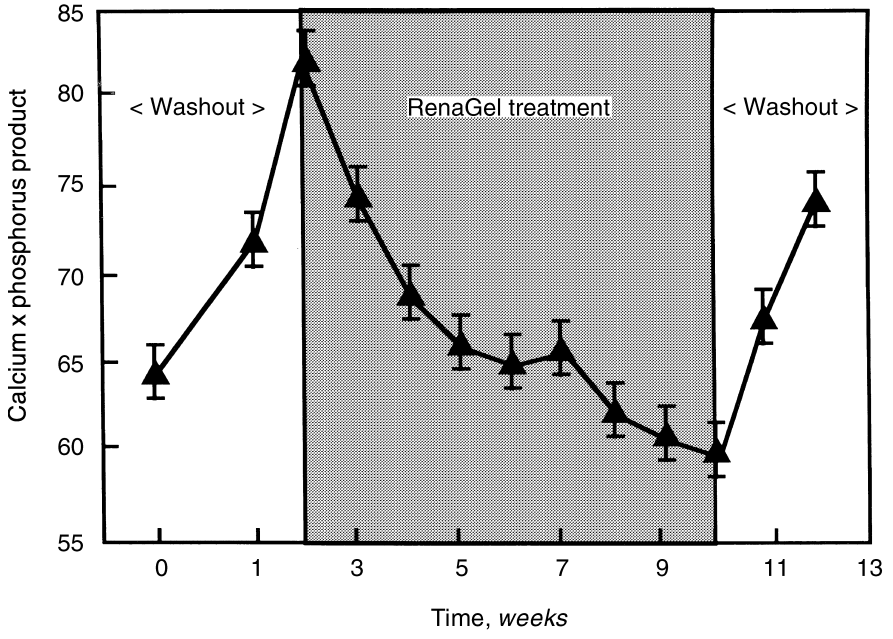

Fig. 4. Effect of RenaGel® on Ca × P product.

± 38.7 mg/dl after eight weeks of treatment ($P < 0.0001$), primarily because of a decrease in mean low-density lipoprotein (LDL) from 102.0 ± 34.9 mg/dl to 75.6 ± 29.4 mg/dl ($P < 0.0001$; Fig. 7). Mean high-density lipoprotein cholesterol and triglycerides did not change during the study. This represents a mean decrease in LDL cholesterol of 15.1% in patients with baseline LDL cholesterol less than 100 mg/dl, and a 29% decrease in patients with baseline LDL cholesterol equal to or greater than 100 mg/dl. No change was observed in serum albumin in either group during RenaGel® treatment.

Safety

RenaGel® was well tolerated. There were no differences across the RenaGel® dose level groups, suggesting that adverse effects were not related to RenaGel® treatment. There were no clinically significant changes in laboratory parameters, including serum chemistries, hepatic function tests, hematologic parameters, coagulation tests, or serum vitamin levels (A-D and E) over the course of the study.

DISCUSSION

The efficacy of currently available calcium- or aluminum-containing phosphate binders is constrained by the side effects associated with the absorption of calcium and aluminum. This study explored the use of RenaGel®, a calcium- and aluminum-free polymeric phosphate binder, in lowering serum phosphorus in hemodialysis

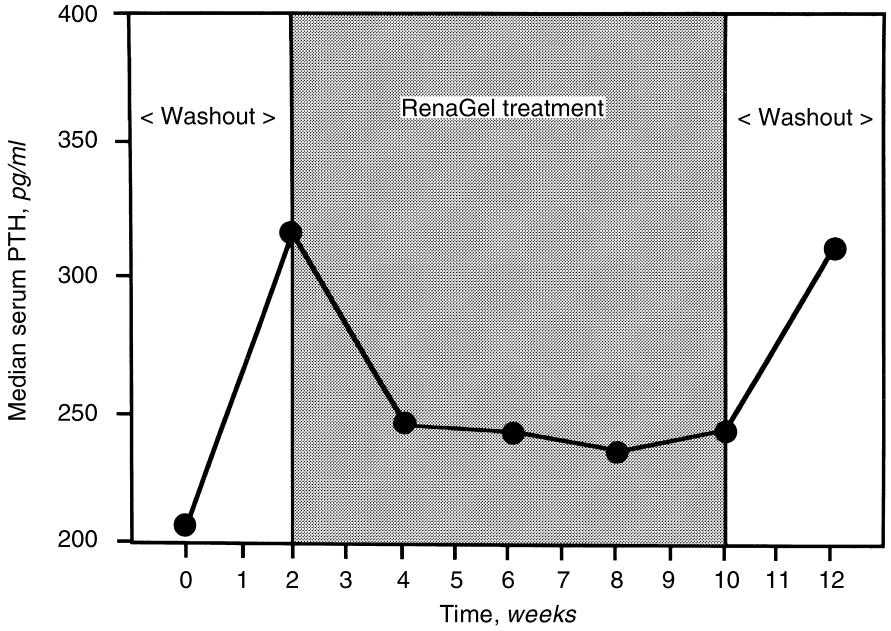

Fig. 5. Effect of RenaGel® on serum parathyroid hormone (PTH). At the end of the 2 week treatment, the decrease in PTH was statistically significant ($P < 0.0001$). After RenaGel was discontinued there was a significant increase in the levels of serum PTH ($P < 0.0001$).

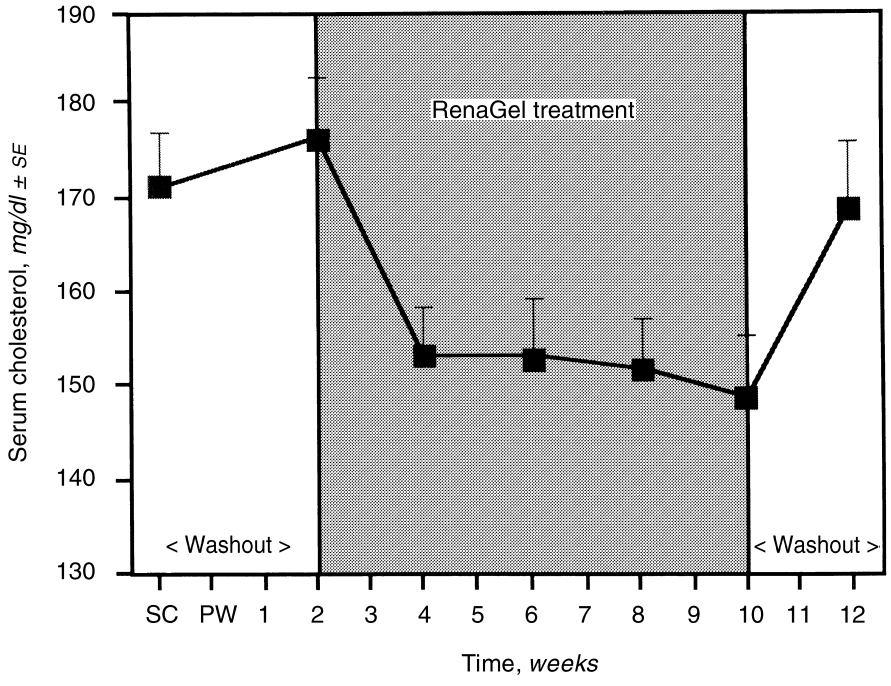

Fig. 6. Effect of RenaGel® on serum total cholesterol.

patients. The primary objectives of this study were to determine the efficacy of RenaGel® treatment in lowering serum phosphorus and the safety of RenaGel® in hemodialysis patients. Secondary objectives were to determine the effect of RenaGel® on serum iPTH and lipid profiles.

RenaGel® significantly reduced serum phosphorus in this hemodialysis patient population. Mean serum phosphorus significantly decreased from 9.1 mg/dl to 6.6 mg/dl ($P < 0.0001$) during eight weeks of RenaGel® treatment and significantly increased after a two-week post-treatment washout ($P < 0.0001$), establishing that the observed lowering of serum phosphorus was due to RenaGel® treatment.

The onset of RenaGel® efficacy was rapid. The initial prescribed RenaGel® dose of two, three, or four capsules

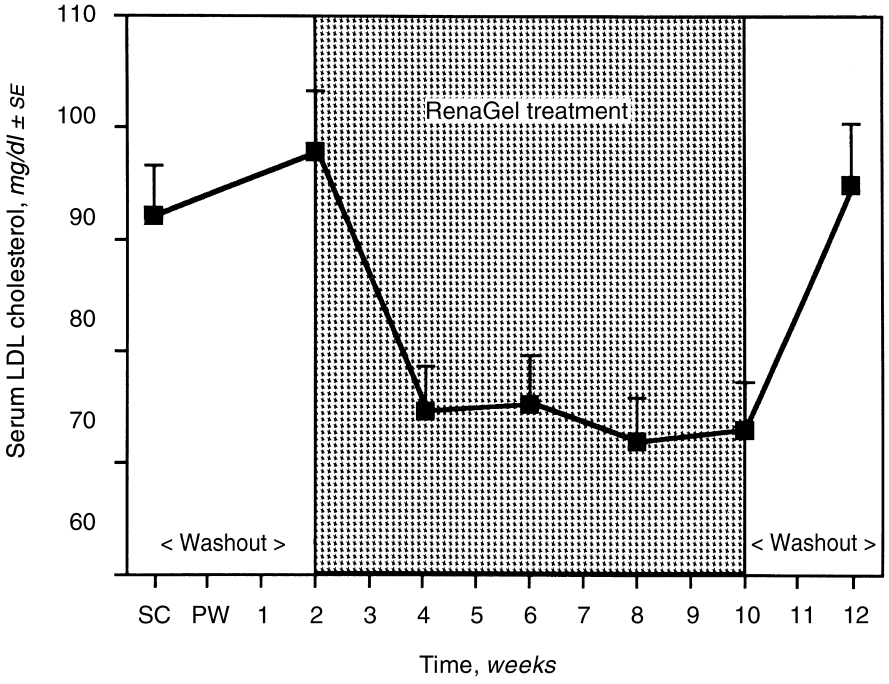

Fig. 7. Effect of RenaGel® on serum low density lipoprotein (LDL). The decrease in LDL was highly statistically significant ($P < 0.0001$).

three times a day with meals substantially reduced serum phosphorus levels within two weeks. Titration of the drug after two and four weeks of treatment led to further reductions; mean serum phosphorus levels returned to prewashout levels by the sixth week of RenaGel® treatment. Based on this study, the anticipated average clinical dose of 5.4 g/day will provide serum phosphorus control comparable to that achieved with currently available calcium-and/or aluminum-based phosphate binders. Greater serum phosphorus reduction was readily attainable with higher doses if escalation was warranted by patient response.

Several investigators have demonstrated in experimental animals [23–27] and *in vitro* studies that phosphorus levels *per se* [independent of serum ionized calcium and $1,25(OH)_2D_3$] increased the synthesis and secretion of PTH. Similar results were shown in uremic patients [28–30]. Moreover, phosphorus also plays an important role in the development of parathyroid cell hyperplasia [25, 26, 31, 32]. Recently, Takahashi et al [33] demonstrated in uremic rats with severe secondary hyperparathyroidism and hyperplasia of the parathyroid glands that when the rats were fed a low-phosphorus diet, the levels of PTH returned to normal. However, the size of the parathyroid glands did not change. Moreover, when intracellular PTH was measured in the parathyroid glands, PTH was the same before or after the administration of a low-phosphorus diet. In other words, it is possible to have hyperplasia of the parathyroid glands without secondary hyperparathyroidism.

If we can extrapolate these results obtained in rats to humans, the control of serum phosphorus is of the utmost importance to prevent increased release of PTH from the parathyroid cells. Several investigators were unable to demonstrate apoptosis of the parathyroid glands in uremic rats treated with $1,25(OH)_2D_3$, low-phosphorus diet, or calcimemtic drugs [25, 33, 34]. Hence, it seems likely that when patients develop severe hyperplasia of the parathyroid glands, although PTH secretion may be temporarily controlled by the administration of a low-phosphorus diet, there remains a potential for rapid and increased secretion of PTH under the right circumstances (such as hyperphosphatemia and/or hypocalcemia). Recently, Kates et al showed that serum phosphorus is independently associated with serum PTH in patients with chronic renal failure [35]. These investigators performed a cross-sectional analysis of 84 patients with varying levels of chronic renal failure. Using stepwise regression analysis after adjusting for multiple comparisons, they found that serum phosphorus correlated directly with serum PTH ($r = 0.62$, $P < 0.01$) in patients with mild to moderate chronic renal failure (creatinine $\leq$ 3.0 mg/dl).

Because calcium acetate and calcium carbonate were discontinued as phosphate binders during the washout period, the observed decline in mean serum calcium in the initial washout period was anticipated. RenaGel® treatment moderately increased serum calcium levels from 9.1 mg/dl to 9.4 mg/dl after eight weeks of treatment ($P = 0.0001$). Several factors could explain this increase in mean serum calcium. First, lowering the serum phosphorus with RenaGel® could have corrected the high

calcium phosphorus product leading to less precipitation of serum calcium [36]. Second, lowering serum phosphorus may have improved the calcemic response to PTH [37]. Third, intestinal phosphate binding by RenaGel® could have increased the intestinal absorption of calcium. Dietary calcium absorption is normally limited by precipitation in the intestine with anions such as phosphate. Notably, despite this increase in serum calcium, mean serum calcium levels never returned to the prewashout levels. The lower serum calcium concentrations might reduce the incidence of hypercalcemia observed during treatment with calcium-based phosphate binders [15–17]. This is of utmost importance in patients with severe hyperparathyroidism (PTH of more than 1,000 pg/ml) because large doses of calcitriol are necessary to suppress the synthesis and secretion of PTH, and the administration of large doses of calcitriol are usually associated with increases in the levels of serum calcium. Because RenaGel® is calcium free, physicians should be able to prescribe calcitriol and evoke less frequent episodes of hypercalcemia.

Serum iPTH levels significantly decreased during RenaGel® treatment. This decline was anticipated because serum calcium and phosphorus are known to regulate PTH secretion [1]. As expected, the increase in serum phosphorus and the decrease in serum calcium during the washout periods prompted a corresponding increase in iPTH.

RenaGel® treatment moderately reduced both serum total cholesterol and LDL cholesterol. RenaGel® treatment had no effect on high-density lipoprotein cholesterol and triglycerides. This cholesterol-lowering effect of RenaGel® was most apparent in patients with LDL cholesterol of 100 mg/dl or greater at baseline and may be beneficial in some patients. Cardiovascular events, mainly related to atherosclerosis, are the most common cause of death in dialysis patients [38, 39]. Longer term studies of lipid lowering in dialysis patients would be required to confirm this potential benefit.

In summary, RenaGel®, a nonabsorbed aluminum- and calcium-free phosphate binder, safely and effectively reduced serum phosphorus in hemodialysis patients. RenaGel® was well tolerated, significantly decreased serum intact PTH, and maintained serum calcium below prewashout levels in hemodialysis patients. It also reduced total and LDL cholesterol. Thus, this new phosphate binder may greatly improve the treatment of secondary hyperparathyroidism in uremic patients.

NOTE ADDED IN PROOF

During the American Society of Nephrology meeting in Philadelphia, October 26, 1998, Dr. G.M. Chertow et al demonstrated that long-term studies with RenaGel® not only decreased LDL by 30%, but increased HDL by 20%. These changes in the lipid profile may lead to important reductions in morbidity in dialysis patients [Chertow GM, Burke SK, Dillon M, Slatopolsky E., for the RenaGel® Study Group: A long-term study of the effectiveness of sevelamer hydrochloride (RenaGel®) in hemodialysis patients. (abstract) *J Am Soc Nephrol* 9:552A, 1998]

ACKNOWLEDGMENTS

This work was supported by a grant provided by Gel-Tex Pharmaceuticals. We thank Sue Viviano for assistance in the preparation of the manuscript.

Reprint requests to: Eduardo Slatopolsky, M.D., Washington University School of Medicine, 660 South Euclid Avenue, Box 8129, St. Louis, MO 63110, USA.
E-mail: eslatopo@imgate.wustl.edu

REFERENCES

1. Coburn JW, Slatopolsky E: Vitamin D, parathyroid hormone and renal osteodystrophy, in *The Kidney* (4th ed), edited by Brenner BM, Rector FC Jr, Philadelphia, Saunders, 1991, pp 2036–2122
2. Delmez J, Slatopolsky E: Hyperphosphatemia: Its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis* 4:303–317, 1992
3. Hou SH, Zhao J, Ellman CF, Hu J, Griffin Z, Spiegel DM, Bourdeau JE: Calcium and phosphorus fluxes during hemodialysis with low calcium dialysate. *Am J Kidney Dis* 18:217–224, 1991
4. Alfrey AC, Le Gendre GR, Kaehney WD: The dialysis encephalopathy syndrome: Possible aluminum intoxication. *N Engl J Med* 315:157–161, 1976
5. Berlyne GM, Ben-Ari J, Pest D, Weinberger J, Stern M, Gilmore GR, Levine R: Hyperaluminaemia from aluminum resins in renal failure. *Lancet* 2:494–496, 1970
6. Felsenfeld AJ, Gutman RA, Llach F, Harrelson JM: Osteomalacia in chronic renal failure; a syndrome previously reported only with maintenance dialysis. *Am J Nephrol* 2:147–154, 1982
7. Griswold WR, Reznik V, Mendoza SA, Trauner D, Alfrey AC: Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. *Pediatrics* 71:56–58, 1983
8. Kaye M: Oral aluminum toxicity in a nondialyzed patient with renal failure. *Clin Nephrol* 20:208–211, 1983
9. Salusky IB, Coburn JW, Paunier L, Sherrard DJ, Fine RN: Role of aluminum hydroxide in raising serum aluminum levels in children undergoing continuous ambulatory peritoneal dialysis. *J Pediatr* 105:717–720, 1984
10. Sherrard DJ, Ott SM, Maloney NA, Andress D, Coburn JW: Uremic osteodystrophy: Classification, cause and treatment, in *Proceedings of the Symposium on Clinical Disorders of Bone and Mineral Metabolism*, edited by Frame B, Potts JT, Amsterdam, Excerpta Medica, 1984, pp 254–258
11. Malluche HH, Smith AJ, Abreo K, Faugere M-C: The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* 311:140–144, 1984
12. Hodsman AB, Sherrard DJ, Alfrey AC, Ott S, Brickman AS, Miller NL, Maloney NA, Coburn JW: Bone aluminum and histomorphometric features of renal osteodystrophy. *J Clin Endocrinol Metab* 54:539–546, 1982
13. Ott SM, Maloney NA, Coburn JW, Alfrey C, Sherrard DJ: The prevalence of bone aluminum in renal osteodystrophy and its relation to the response to calcitriol therapy. *N Engl J Med* 307:709–713, 1982
14. Moriniere PH, Russel A, Tahiri Y, Fremont JF, Maurel G, Jaudon MC, Gueris J, Fournier A: Substitution of aluminum hydroxide by high doses of calcium carbonate in patients on chronic hemodialysis: Disappearance of hyperaluminemia and equal con-

trol of hyperparathyroidism. *Proc Eur Dial Transplant Assoc* 19:784–787, 1982
15. Fournier A, Moriniere P, Sebert JL, Dhissi H, Atik A, Leflon P, Renaud H, Gueris J, Gregoire I, Idrissi A, Garabedian M: Calcium carbonate, an aluminum-free agent for control of hyperphosphatemia, hypocalcemia and hyperparathyroidism. *Kidney Int* 29:S114–S119, 1986
16. Salusky IB, Coburn JW, Foley J, Nelson P, Fine RN: Oral calcium carbonate as a phosphate-binding agent in children on dialysis: Effect on plasma aluminum levels. *J Pediatr* 108:767–770, 1986
17. Slatopolsky E, Weerts C, Lopez-Hilker J, Norwood K, Zink M, Windus D, Delmez J: Calcium carbonate as a phosphate-binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 315:157–161, 1986
18. Hercz G, Kraut JA, Andress DA, Howard N, Roberts C, Shinaberger JH, Sherrard DF, Coburn JW: Use of calcium carbonate as a phosphate-binder in dialysis patients. *Miner Electrolyte Metab* 12:314–319, 1986
19. Rosenbaum DP, Holmes-Farley WH, Manderville M, Goldberg DI: Effects of RenaGel®, a nonabsorbable, cross-linked, polymeric phosphate binder on urinary phosphorus excretion in rats. *Nephrol Dial Transplant* 11:808–812, 1996
20. Burke SK, Slatopolsky E, Goldberg DI: RenaGel®, a novel calcium-and aluminum-free phosphate binder, inhibits phosphate absorption in normal volunteers. *Nephrol Dial Transplant* 12:1640–1644, 1997
21. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, Bonventre J, Slatopolsky E: Poly [alkylamine hydrochloride] RenalGel®: A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 1:66–71, 1997
22. Posner BM, Borman CL, Morgan JL, Borden WS, Ohls JG: The validity of a telephone-administered 24-hour dietary recall methodology. *Am J Clin Nutr* 36:546–553, 1982
23. Lopez-Hilker SA, Dusso A, Rapp N, Martin KJ, Slatopolsky E: Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol. *Am J Physiol* 259:F432–F437, 1993
24. Yi H, Fukagawa M, Yamamoto H, Kumagai M, Watanabe T, Kurokawa K: Prevention of enhanced parathyroid hormone secretion, synthesis and hyperplasia by mold dietary phosphorus restriction in early chronic renal failure in rats: Possible direct role of phosphorus. *Nephron* 70:242–248, 1995
25. Naveh-Many T, Rahamimo R, Livni N, Silver J: Parathyroid cell proliferation in normal and chronic renal failure rats: The effects of calcium, phosphate and vitamin D. *J Clin Invest* 96:1786–1793, 1995
26. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, MacDonald P, Brown AJ: Phosphorus restriction prevents parathyroid gland growth: High phosphorus directly stimulates PTH secretion in vitro. *J Clin Invest* 97:2534–2540, 1996
27. Almaden Y, Canalejo A, Hernandez A, Ballesters E, Garcia-Navarro S, Torres A, Rodriguez M: Direct effect of phosphorus on PTH secretion from whole rat parathyroid glands in vitro. *J Bone Miner Res* 11:970–976, 1996
28. Lucas PA, Brown RC, Woodhead JS, Coles GA: 1,25-Dihydroxycholecalciferol and parathyroid hormone in advanced chronic renal failure: Effect of simultaneous protein and phosphorus restriction. *Clin Nephrol* 25:7–10, 1986
29. Schaefer K, Erley CM, von Herrath D, Stein G: Calcium salts of ketoacids as a new treatment strategy for uremic hyperphosphatemia. *Kidney Int* 36:S136–S139, 1989
30. Aparicio M, Combe C, Lafage MH, DePecigout V, Potaux L, Bourchet JL: In advanced renal failure, dietary phosphorus restriction reverses hyperparathyroidism independent of the levels of calcitriol. *Nephron* 63:122–123, 1994
31. Wang O, Palnitkar S, Parffitt AM: Parathyroid cell proliferation in the rat. Effect of age and phosphate administration and recovery. *Endocrinology* 137:4558–4562, 1996
32. Parfitt AM: The hyperparathyroidism of chronic renal failure: A disorder of growth. *Kidney Int* 52:3–9, 1997
33. Takahashi F, Finch J, Brown AJ, Slatopolsky E: The effects of a low phosphorus diet on the section of PTH in establishing diffuse parathyroid hyperplasia. (abstract) *J Am Soc Nephrol* 8:508A, 1997
34. Wada M, Furuya Y, Sakiyama J, Kobayashi N, Miayata S, Ishii H, Nagano N: The calcimimetic compound NPS R-68 suppresses parathyroid cell proliferation in rats with renal insufficiency: Control of parathyroid cell growth via a calcium receptor. *J Clin Invest* 100:2877–2983, 1997
35. Kates DM, Sherrard DJ, Andress DL: Evidence that serum phosphate is independently associated with serum PTH in patients with chronic renal failure. *Am J Kidney Dis* 30:809–813, 1997
36. Katz A, Hampers CL, Merrill JP: Secondary hyperparathyroidism and renal osteodystrophy in chronic renal failure. *Medicine* 48:333–374, 1969
37. Rodriguez M, Martin-Malo A, Martinez MD, Torres A, Felsenfeld AJ, Llac F: Calcemic response to parathyroid hormone in renal failure: Role of phosphorus and its effects on calcitriol. *Kidney Int* 40:1055–1062, 1991
38. Bomer J, Stroheck E, Goerich J, Babner M, Zuna I: Arteriosclerosis in dialysis patients. *Int J Artif Organs* 19:638–644, 1996
39. United States Renal Data System: *USRDS 1997 Annual Report.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD, 1997, 93 pp.